REMARKS

The claims are 1, 4 and 7-11. Claims 5, 6 and 47 have been cancelled. Claim 1 has been amended by adding the limitations of claims 5 and 47 thereto. Accordingly, this change is not new matter. Favorable consideration of the presently amended claims is respectfully requested.

The undersigned would like to thank the Examiner for the kind courtesy of the interview of December 2, 2004. During the interview the Examiner agreed that support from claim 4 could be found at page 7, lines 18-20 and thus the rejection under 35 U.S.C. §112 would be withdrawn.

In addition, during the interview, the rejection of claims 1, 4 and 10 as allegedly being anticipated under U.S. Patent No. 2,156,599 (Mieschner) or U.S. Patent No. 3,478,070 (Stein) was discussed. Applicants submitted that a solid dosage form of estradiol-3-acetate with a pharmaceutically acceptable carrier was not disclosed by either. The Examiner believed that Example 1 of Mieschner could be construed as disclosing estradiol-3-acetate with methanol as a carrier because some residual methanol could be present after crystallization. While Applicants disagree with the propriety of this rejection, to expedite prosecution, Applicants have amended claim 1 by bringing in the limitation of claim 5, i.e., the amount of estradiol-3-acetate present, to clearly differentiate the claimed invention from the cited art. The Examiner agreed during the interview that this change would obviate the rejection under 35 U.S.C. §102(b).

The rejection of the claims under 35 U.S.C. §103 as allegedly being obvious over Stein further in view of March and Wolfe was then discussed at the December 2, 2004 interview. Dr. deVries explained to the Examiner that it was unexpectedly discovered that estradiol acetate had a significantly improved bioavailability compared to estradiol. The improvement is described in Dr. deVries Declaration of November 14, 2003. Because of this improved bioavailability a patient can be treated with essentially 22% less estradiol using the solid dosage of this invention and still obtain the same effect that would be obtained with an estradiol solid dosage. As the Examiner is well aware the ability to reduce the exposure of a woman to estrogen while still achieving the same beneficial effect is a highly significant advantage.

It was, however, also explained to the Examiner that estradiol-3-acetate degrades significantly when exposed to moisture. The Examiner indicated that he believed it was well known that esters hydrolyze in the presence of water. Dr. deVries, however, pointed out to the

Examiner that the degree of hydrolysis would differ significantly from compound to compound and noted, for example, that norethindrone acetate, does not suffer from the same extent of water hydrolysis degradation that has been found with estradiol acetate. The present invention recognizes that to obtain the improved bioavailability advantage of the solid dosage form of this invention that the stability of the estradiol-3-acetate must be maintained. One manner of maintaining stability in the present invention is to control the moisture level in the solid dosage. The present claim requires the percent moisture of the dosage unit to be less than or equal to 8%. The Examiner requested data to show the criticality of moisture limitation. While Applicants believe that the present specification makes clear the significance of controlling moisture in the solid dosage unit, Applicants intend to run tests and present them in a continuation application including claims whereby the stability of the estradiol-3-acetate is controlled by limitation of the moisture.

However, to expedite allowance of the present application, Applicants have amended the claims to include the ester hydrolysis inhibitor acetic acid which has been found to have a significant stabilizing effect. The criticality of the acetic acid can be seen in the Declaration of Dr. deVries dated May 25, 2004. As can be seen from Table 1 of that Declaration, solid dosage tablets of this invention containing estradiol acetate and acetic acid were significantly superior in initial and ongoing stability compared to the formulation that did not contain acetic acid. As discussed above, to obtain the benefit of the improved bioavailability of estradiol achieved with an estradiol acetate solid dosage formulation, the stability of the estradiol acetate must be maintained.

Neither Stein nor Meischner disclose a stabilized solid dosage form of estradiol-3-acetate, let alone a solid dosage form that contains acetic acid as an ester hydrolysis inhibitor. As previously noted, Applicants respectfully submit that March does not remedy the deficiencies of Stein or Mieschner. First, March indicates that bases and acids can cause ester hydrolysis. Moreover, even if one were to consider the equilibrium state described in March, it is clear that the extent of the equilibrium state for each compound can differ significantly, e.g. compare estradiol-3-acetate to norethindrone acetate. Thus, Applicants respectfully submit that it is only in hindsight that one of ordinary skill in the art would find a suggestion in March to stabilize a solid dosage of estradiol-3-acetate with acetic acid. None of the cited prior art recognized the advantage of using estradiol-3-acetate due to its enhanced bioavailability, nor the problem of

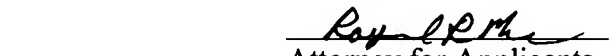
estradiol-3-acetate instability and thus cannot be said to suggest the solution to harness this unexpected advantage.

Applicants respectfully submit that the present invention, and the advantages achieved thereby, are not disclosed or suggested by the art of record. Moreover, even if the Examiner deems that the art of record allows for a prima facie case of obviousness, it is respectfully submitted that such a conclusion is clearly rebutted by the unexpected advantage achieved by the presently claimed solid dosage formulation.

Wherefore, the art of record does not disclose or suggest the presently claimed invention, whether taken alone or together. Accordingly, Applicants respectfully request that the claims be allowed and the case passed to issue.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,



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